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ORIGINAL CONTRIBUTIONS

Parental Occupational Exposures to Chemicals and Incidence of Neuroblastoma in Offspring

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To evaluate the effects of parental occupational chemical exposures on incidence of neuroblastoma in offspring, the authors conducted a multicenter case-control study, using detailed exposure information that allowed examination of specific chemicals. Cases were 538 children aged 19 years who were newly diagnosed with confirmed neuroblastoma in 1992–1994 and were registered at any of 139 participating hospitals in the United States and Canada. One age-matched control for each of 504 cases was selected through random digit dialing. Self-reported exposures were reviewed by an industrial hygienist, and improbable exposures were reclassified. Effect estimates were calculated using unconditional logistic regression, adjusting for child's age and maternal demographic factors. Maternal exposures to most chemicals were not associated with neuroblastoma. Paternal exposures to hydrocarbons such as diesel fuel (odds ratio (OR) = 1.5; 95% confidence interval (CI): 0.8, 2.6), lacquer thinner (OR = 3.5; 95% CI: 1.6, 7.8), and turpentine (OR = 10.4; 95% CI: 2.4, 44.8) were associated with an increased incidence of neuroblastoma, as were exposures to wood dust (OR = 1.5; 95% CI: 0.8, 2.8) and solders (OR = 2.6; 95% CI: 0.9, 7.1). The detailed exposure information available in this study has provided additional clues about the role of parental occupation as a risk factor for neuroblastoma. *Am J Epidemiol* 2001;154:106–14.

child; dust; hydrocarbons; metals; neuroblastoma; occupational exposure

Understanding of the molecular biology and genetics of neuroblastoma has advanced considerably in recent years, but comparatively little is known about its possible environmental etiology. Several studies have examined the association of neuroblastoma with parental occupation (1–5). In these studies, exposures were usually inferred from job titles rather than from descriptions of duties or self-reported exposures. Associations with paternal work in farming and parental (maternal or paternal) work as an electrician or in electronics assembly and repair were reported (2, 3). Jobs with potential exposure to dusts, metals, or hydrocarbons were associated with increased incidence in some studies (2, 3, 5) but not in others (1, 4, 5). Although results from these studies are suggestive, the studies were limited with respect to sample size and assessment of occupational exposures.

To evaluate the effects of parental occupational exposures on neuroblastoma incidence in offspring, we conducted a large, multicenter case-control study. Our first analysis examined incidence by parental job title (6). It found an increased rate of neuroblastoma for parents working as electrical power installers or power plant operators, for mothers working as hairdressers, and for fathers working as firefighters, landscapers, mechanics, painters, glass and optical goods workers, or broadcast, telephone, and dispatch operators. In this paper, we report results from further analysis of the same study population. We employed detailed exposure assessment that allowed estimation of the effects of specific occupational chemical exposures, using information on job title as well as on self-reported duties and exposures.

MATERIALS AND METHODS

Study population

Eligible cases were patients under the age of 19 years who had a confirmed new diagnosis of neuroblastoma between May 1, 1992, and April 30, 1994, and were registered at any of 139 participating hospitals in the United

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Abbreviations: CI, confidence interval; IH, industrial hygienist; OR, odds ratio.

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States and English-speaking Canada. The hospitals were members of either of two pediatric collaborative clinical trials groups: the Children's Cancer Group or the Pediatric Oncology Group. A total of 741 potentially eligible case children were identified. The treating physicians provided permission to approach the parents for participation in the study. Following the physician's consent, further criteria for inclusion of eligible cases were that the biologic mother was available for interview in either English or Spanish and that the case household had a telephone. Of the families contacted, we enrolled 538 cases (73 percent of those eligible). Nonparticipation of cases was primarily due to physician refusal (12 percent) and maternal refusal (8 percent). The 538 enrolled neuroblastoma cases had ages at diagnosis that ranged from newborn to 17 years, with a mean of 2.2 years; 56 percent of case children were male. N-*myc* copy number, determined by Southern blot (7) or fluorescence in situ hybridization (8), indicated amplification of the N-*myc* oncogene in 71 of 408 tumors analyzed (17 percent).

One control was selected for each of 504 cases through random digit dialing. We were unable to identify controls for the remaining 34 cases after multiple attempts. Controls were individually caliper-matched to cases on date of birth (±6 months for cases ≤3 years of age, ±1 year for cases >3 years of age). The response proportion for the random digit dialing screening was 74 percent, calculated as the percentage of households that participated out of the total number selected for screening (9), and recruitment among eligible controls was 71 percent.

Data collection

A telephone interview was conducted with each mother, as well as with the father when he was available. We obtained interviews from 472 case fathers (88 percent of enrolled cases; 405 direct interviews and 67 proxy interviews with the mother) and 445 control fathers (88 percent of enrolled controls; 304 direct interviews and 141 proxy interviews with the mother). The interview included questions on demographic characteristics such as parental age, race, education, and income. Information on occupational history was obtained from each parent, including dates of employment, names of employers, occupations, industries, job titles, specific duties, and hours per week. For each job held during the 2-year period prior to the child's date of birth, mothers and fathers were asked if they had been exposed to chemicals, dusts, fumes, gases, vapors, or oils. Respondents could report exposure to any of 65 chemicals, compounds, or broad categories of substances listed in an interview guide that was provided. For each chemical exposure reported in each job, data were collected on the form of exposure (gas or vapor, dust or powder, smoke, liquid, or solid), the route of exposure (air, skin, clothing, swallowing), the work activities being performed during exposure (e.g., working near exposure, cleaning, wiping, cutting), the number of hours of exposure per week, and the dates on which exposure began and ended.

Information on occupational chemical exposure was available for 1,040 mothers (537 case mothers and 503 control mothers; 503 matched pairs) and 707 fathers (405 case fathers and 302 control fathers; 232 matched pairs). These numbers are lower than the total number of interviews completed, primarily because proxy respondents for fathers' interviews were not asked questions from the occupational history section on chemical exposures. Proxy-reported information on occupational exposure is subject to misclassification due to low sensitivity and low positive predictive value (10, 11); therefore, we did not consider it reliable. Additionally, two mothers and three fathers refused to answer the questions on occupational chemical exposure.

Exposure assessment

Parental occupational chemical exposure was coded in several ways.

Self-reported exposures. A parent was coded as having been exposed to a substance if he or she reported exposure to that substance in any job.

Industrial hygienist's review of self-reported exposures. We reviewed each reported exposure scenario carefully under the supervision of an industrial hygienist (K. Teschke), so that any situation in which exposure was improbable was recoded as unexposed. All exposure coding was conducted without knowledge of subject's disease status or parent's gender. In community-based case-control studies in which the prevalence of most exposures is low (<15 percent), incorrectly classifying even small numbers of individuals as exposed results in bias that substantially attenuates effect estimates toward the null value, if the misclassification is nondifferential and there is a true positive association; whereas an equal proportion of individuals incorrectly classified as unexposed will contribute little bias to the estimate (12–14). In order to minimize bias resulting from exposure misclassification, our industrial hygienist (IH) review focused on increasing the specificity of exposure measures by reducing the number of false-positive exposures. Jobs in which no chemical exposure was reported were not reviewed. All reported information for each exposure was reviewed, including occupation, industry, hours of exposure per week, form of the substance, route of exposure, use of protective equipment or clothing, and specific work activities. A parent was coded as having been exposed to a chemical if the IH review determined probable exposure in any job.

Chemical categories. Chemicals were grouped into five broad categories to allow evaluation of the effect of chemicals with similar physicochemical characteristics and for comparability of results with the findings of previous studies. Data on exposures to sufficiently common specific chemicals were retained for analyses, but these substances were also grouped into the following categories: halogenated hydrocarbons; nonvolatile hydrocarbons; volatile hydrocarbons; paints, inks, and pigments; and metals, alloys, and solders (see table 1).

Coding of covariates

Demographic characteristics of interest included maternal education, maternal race, and maternal age at the birth of the

TABLE 1. Categories of chemicals* evaluated in a study of parental occupational exposures and neuroblastoma in offspring, United States and Canada, 1992–1994

Halogenated hydrocarbons	Nonvolatile hydrocarbons	Volatile hydrocarbons	Paints, inks, and pigments	Metals, alloys, and solders
Degreasers or dry cleaning agents (NOS†)	Petroleum products, oils, and lubricants (NOS)	Solvents or paint thinners (NOS)	Paints, inks, and pigments (NOS)	Metals, alloys, and solders (NOS)
Carbon tetrachloride	Cutting oil	Acetone	Oil-based or solvent-based paints, inks, or pigments	Alloys (NOS)
Chloroform	Diesel fuel	Alcohols	Water-based (latex) paints, inks, or pigments	Metals (NOS)
Ethylene dichloride	Kerosene	Benzene		Solders (NOS)
Freon	Lubricating oil or grease	Carbon disulfide		Brass
Methylene chloride		Cellosolve		Bronze
Perchloroethylene		Gasoline		Galvanized iron or steel
Trichloroethylene		Glycols or glycol ethers		High-speed steel
Valclene or trichlorotrifluoroethane		Lacquer thinner		Mild steel
		Methyl ethyl ketone		Stainless steel
		Naphtha		Stellite
		Paint thinner		Tungsten carbide
		Phenol		
		Toluene		
		Turpentine		
		Varsol or mineral spirits		
		White gas		
		Xylene		

* Other chemicals analyzed but not included in categories: plastics, synthetics, or resins (NOS); animal fur or feather dust; cardboard dust; flour or starch dust; grain dust; rubber dust; and wood dust.
† NOS, not otherwise specified.

index child. These factors were coded using indicator variables with the following categories: for maternal education, less than high school graduation, high school graduation and/or some college, and college degree or more (referent); for maternal race, White (referent), Black, Hispanic, and other; and for maternal age at the birth of the index child, <18 years, 18–39 years (referent), and ≥40 years.

Statistical analyses

Separate analyses were conducted for maternal and paternal exposures to each chemical. Where the overall frequency of IH-reviewed exposure among cases and controls was five or greater, we calculated exposure odds ratios to estimate the incidence rate ratios for neuroblastoma associated with self-reported and IH-reviewed exposure. Each chemical exposure was evaluated in a separate model, using persons unexposed to the chemical as the reference group. Exposure odds ratios were calculated using unconditional logistic regression modeling so that all matched and unmatched subjects could be included to enhance precision. Each model included variables for the matching factor, child's age, which was coded as a set of indicator variables (6-month intervals for ages ≤3 years; 2-year intervals for ages >3–11 years; one variable for ages >11 years), as well as variables for the set of demographic covariates. We conducted separate analyses to evaluate associations between parental occupational chemical exposures and specific subtypes of neuroblastoma, as defined by age at diagnosis (≤1 year vs. >1 year) or N-*myc* oncogene status (amplified vs. normal).

We considered confounding among certain groups of paternal occupational chemical exposures that frequently occurred together (i.e., 10 or more fathers in the study were exposed to both of two chemicals). Frequent co-occurrence was common among the following groups of chemicals, which were evaluated in three separate models: 1) hydrocarbons with paints; 2) wood dust with paints and hydrocarbons; and 3) four types of steel alloys and solders (not otherwise specified) with lubricating and cutting oils. Confounding was examined by modeling all relevant exposures simultaneously, along with variables for child's age and the demographic covariates. Maternal exposures were too infrequent to allow examination of confounding by specific chemicals.

RESULTS

The distributions of selected characteristics in the entire study population and in the subset of fathers with exposure information are shown in table 2. Matching ensured an equitable distribution of child's age between cases and controls, although the distribution differed in the subset of fathers with chemical exposure information; specifically, the controls were slightly younger than these cases. Cases were more likely than controls to be male. Mothers of cases were more likely to be younger than 18 years or older than 40 years at the time of the child's birth, and they were less likely to be college graduates than were mothers of controls. Maternal race was similar for cases and controls.

The frequencies and effect estimates for maternal and paternal occupational chemical exposures are shown in tables 3 and 4. Chemicals with IH-reviewed exposure frequencies below five were not analyzed further and are therefore not listed in the tables, although they were included in the chemical category frequencies. Very few mothers reported having occupational exposure to chemicals. In

TABLE 2. Characteristics of the study population, by child's disease status, in a study of parental occupational chemical exposures and neuroblastoma in offspring, United States and Canada, 1992–1994

Characteristic	Total study population (n = 1,042)		Subset with completed interviews for analysis of fathers' exposures (n = 707)	
	Cases (n = 538)	Controls (n = 504)	Cases (n = 405)	Controls (n = 302)
Child				
Mean age (years)	2.2 (2.4)*	2.2 (2.5)	2.2 (2.4)	2.1 (2.3)
Age (%)				
≤1 year	38.8	39.1	39.7	42.3
>1 year	61.2	60.9	60.3	57.7
Sex (%)				
Male	55.9	50.2	54.8	51.0
Female	44.1	49.8	45.2	49.0
Mother				
Race (%)				
White	79.7	78.6	85.2	86.1
Black	7.8	7.7	4.4	4.0
Hispanic	9.1	10.7	7.9	7.6
Other	3.3	3.0	2.5	2.3
Mean age (years) at birth of child	27.2 (5.6)	27.7 (5.3)	28.0 (5.4)	28.6 (4.9)
Age at birth of child (%)				
<18 years	3.5	1.2	2.2	1.0
18–39 years	94.4	97.4	95.3	98.0
≥40 years	2.0	1.4	2.5	1.0
Education (%)				
Less than high school graduation	11.2	10.1	7.7	5.6
High school graduation	68.0	63.1	67.4	62.6
College graduation or more	20.8	26.8	24.9	31.8

* Numbers in parentheses, standard deviation.

addition, where maternal exposures were reported, they frequently occurred in activities that were less likely to have high exposure; therefore, these mothers were recoded as unexposed. For both mothers and fathers, the frequency of reporting of individual chemical compounds (e.g., benzene) was not as high as the reporting of chemical products with well-known common names (e.g., gasoline). Given that individual chemical compounds such as benzene constitute a small component of chemical products such as gasoline, these individual chemical compounds are likely to have been underreported. The exposure frequencies were adequate for analyses of 46 paternal exposures and 17 maternal exposures to chemicals or categories. Because there were virtually no differences between crude and adjusted effect estimates, only adjusted estimates are presented in the tables. Effects of parental occupational chemical exposures on the incidence of neuroblastoma in offspring were evaluated primarily by means of the adjusted odds ratios for IH-reviewed exposure.

There was little evidence that any of the maternal exposures were associated with an increased incidence of neuroblastoma in offspring (see table 3), although there was an excess of case mothers who had been exposed to animal fur or feather dust (five cases and no controls).

Paternal occupational exposures to several chemicals were associated with increased incidence of neuroblastoma in offspring (see table 4). Odds ratios for several hydrocarbons were 1.5 or above, including alcohols, benzene, cutting oil, diesel fuel, lacquer thinner, mineral spirits, paint thinner, and turpentine. Odds ratios for the categories of volatile hydrocarbons (odds ratio (OR) = 1.5; 95 percent confidence interval (CI): 1.0, 2.1) and nonvolatile hydrocarbons (OR = 1.5; 95 percent CI: 1.0, 2.2) were elevated as well. The data indicated positive associations between neuroblastoma and paternal exposures to certain metals, alloys, and solders, including stainless steel, mild steel, galvanized steel, high-speed steel, brass, metals (not otherwise specified), and solders (not otherwise specified), although exposure to metals, alloys, and solders as a category was not strongly associated with neuroblastoma. There was a 50 percent increased incidence of neuroblastoma associated with paternal exposure to wood dust. Of the other dust exposures analyzed, odds ratios were elevated for grain dust and rubber dust, although the estimates were extremely imprecise. When separate analyses were conducted by N-*myc* oncogene status or age at diagnosis, there did not appear to be a specific subtype of neuroblastoma with which paternal occupational chemical exposures were more or less strongly associated (results not shown).

TABLE 3. Estimated effects of maternal occupational exposures to chemicals on the incidence of neuroblastoma in offspring,* United States and Canada, 1992–1994

Chemical†	Self-reported exposure				IH‡-reviewed exposure			
	No. exposed		Adjusted§ odds ratio	95% CI‡	No. exposed		Adjusted§ odds ratio	95% CI
	Cases	Controls			Cases	Controls		
Halogenated hydrocarbons	15	19	0.7	0.4, 1.5	6	8	0.7	0.2, 2.1
Nonvolatile hydrocarbons	26	20	1.2	0.7, 2.2	12	10	1.1	0.5, 2.5
Diesel fuel	12	9	1.3	0.5, 3.1	3	3	0.9	0.2, 4.4
Lubricating oil	14	9	1.4	0.6, 3.4	5	7	0.6	0.2, 2.0
Volatile hydrocarbons	55	40	1.4	0.9, 2.1	27	22	1.2	0.7, 2.1
Acetone	18	13	1.3	0.6, 2.7	9	8	1.1	0.4, 2.8
Alcohols	19	20	0.9	0.5, 1.7	14	14	1.0	0.5, 2.1
Gasoline	14	8	1.6	0.6, 3.8	3	3	0.8	0.2, 4.2
Lacquer thinner	8	4	1.9	0.6, 6.4	3	2	1.5	0.2, 9.2
Paint thinner	14	11	1.2	0.6, 2.7	3	3	0.9	0.2, 4.6
Paints, inks, and pigments	21	20	1.0	0.5, 1.9	7	12	0.6	0.2, 1.4
Oil-based paints	15	13	1.1	0.5, 2.4	2	8	0.2	0.1, 1.1
Water-based paints	13	10	1.2	0.5, 2.7	5	4	1.2	0.3, 4.7
Metals, alloys, and solders	9	10	0.9	0.3, 2.1	1	1	0.8	0.1, 13.0
Other								
Animal fur or feather dust	5	0	∞		5	0	∞	
Cardboard dust	12	11	1.0	0.4, 2.3	7	7	0.9	0.3, 2.6
Flour or starch dust	2	8	0.3	0.1, 1.2	1	6	0.2	0.0, 1.4

* The analysis included 537 case mothers and 503 control mothers.
† Main entries indicate categories of chemicals analyzed as groups (from table 1).
‡ IH, industrial hygienist; CI, confidence interval.
§ Adjusted for child's age, maternal race, maternal age, and maternal education.

Analyses of paternal exposures that frequently occurred together revealed some confounding between different groups of chemicals. When data were simultaneously adjusted for paternal exposures to frequently co-occurring hydrocarbons and paints, odds ratios for alcohols (OR = 1.6; 95 percent CI: 0.7, 3.4), diesel fuel (OR = 2.0; 95 percent CI: 1.0, 4.3), lacquer thinner (OR = 2.9; 95 percent CI: 1.0, 8.3), mineral spirits (OR = 1.7; 95 percent CI: 0.6, 4.5), and turpentine (OR = 12.0; 95 percent CI: 2.2, 65.9) remained elevated, whereas the odds ratio for paint thinner was diminished (OR = 0.9; 95 percent CI: 0.4, 2.1). The odds ratio for paternal exposure to wood dust was elevated (OR = 1.6; 95 percent CI: 0.8, 3.0), even after adjustment for potential confounding by exposure to hydrocarbons or paints. When four steel alloys and solders (not otherwise specified) were included in the same model as cutting and lubricating oils, the effect estimate for solders remained moderately elevated (OR = 2.5; 95 percent CI: 0.8, 7.6), whereas the estimates for the steel alloys were too imprecise for evaluation of confounding.

DISCUSSION

There are several mechanisms by which parental chemical exposures might increase the risk of neuroblastoma in offspring. According to Knudson's two-stage model of carcinogenesis, a minimum of two mutations or inactivating events in a crucial gene are required for carcinogenesis (15, 16). These mutations could occur during gametogenesis in the mother or father and would then be inherited by the child, or they could occur sporadically in target tissues of the developing fetus or child. Exposures of concern to the mother or father are likely to occur at different time points relative to conception. During the period of gametogenesis prior to conception, paternal exposures could cause a germline mutation in sperm DNA. There are human data demonstrating that paternal exposures can cause mutations in sperm DNA, and animal models provide some evidence that paternal exposures can increase the risk of cancer in offspring via mutations in the germ cell line (17–19). Maternal exposures are of particular concern during pregnancy, because in-utero exposure of the fetus could occur by means of chemicals crossing the placenta. Although we wished to examine the effects of parental occupational chemical exposures during the specific time periods of preconception and pregnancy, exposures overlapped the different periods and therefore did not support comparative analyses.

Several of the paternal exposures associated with elevated effect estimates in our study are hydrocarbons. In a previous study, Spitz and Johnson (3) observed an increased rate of neuroblastoma associated with job clusters linked to moderate exposures to aromatic and aliphatic hydrocarbons. This

TABLE 4. Estimated effects of paternal occupational exposures to chemicals on the incidence of neuroblastoma in offspring,* United States and Canada, 1992–1994

Chemical†	Self-reported exposure				IH‡-reviewed exposure			
	No. exposed		Adjusted§ odds ratio	95% CI‡	No. exposed		Adjusted§ odds ratio	95% CI
	Cases	Controls			Cases	Controls		
Halogenated hydrocarbons	75	48	1.2	0.8, 1.7	34	26	0.9	0.5, 1.5
Carbon tetrachloride	7	11	0.4	0.2, 1.2	4	4	0.6	0.2, 2.6
Chloroform	6	5	1.0	0.3, 3.2	3	2	1.2	0.2, 7.5
Freon	29	23	0.9	0.5, 1.7	9	13	0.5	0.2, 1.1
Methylene chloride	10	11	0.7	0.3, 1.6	4	4	0.7	0.2, 2.8
Perchloroethylene	8	11	0.5	0.2, 1.4	4	6	0.5	0.1, 1.7
Trichloroethylene	22	12	1.4	0.7, 2.9	9	7	0.9	0.3, 2.5
Nonvolatile hydrocarbons	130	78	1.3	0.9, 1.9	91	48	1.5	1.0, 2.2
Cutting oil	40	27	1.1	0.6, 1.8	16	7	1.7	0.7, 4.2
Diesel fuel	72	44	1.2	0.8, 1.9	42	21	1.5	0.8, 2.6
Kerosene	26	18	1.1	0.6, 2.0	16	11	1.0	0.5, 2.2
Lubricating oil	79	50	1.2	0.8, 1.8	56	36	1.1	0.7, 1.8
Volatile hydrocarbons	175	114	1.2	0.9, 1.7	122	67	1.5	1.0, 2.1
Acetone	41	34	0.9	0.5, 1.5	23	19	0.9	0.5, 1.7
Alcohols	49	37	1.0	0.6, 1.6	35	16	1.8	0.9, 3.3
Benzene	11	8	1.0	0.4, 2.6	5	2	2.0	0.4, 10.3
Gasoline	77	66	0.8	0.5, 1.2	45	38	0.8	0.5, 1.3
Glycols	16	11	1.1	0.5, 2.4	7	4	1.3	0.4, 4.6
Lacquer thinner	49	17	2.4	1.3, 4.2	36	8	3.5	1.6, 7.8
Methyl ethyl ketone	19	16	0.9	0.4, 1.7	12	6	1.4	0.5, 3.8
Mineral spirits	40	18	1.8	1.0, 3.2	26	9	2.2	1.0, 4.9
Naphtha	11	8	1.0	0.4, 2.5	6	3	1.4	0.4, 5.9
Paint thinner	65	35	1.4	0.9, 2.2	43	17	1.9	1.0, 3.4
Toluene	16	14	0.8	0.4, 1.7	10	7	1.0	0.4, 2.7
Turpentine	32	14	1.9	1.0, 3.6	25	2	10.4	2.4, 44.8
White gas	9	9	0.7	0.3, 1.9	5	3	1.2	0.3, 5.3
Xylene	15	9	1.3	0.5, 3.0	10	5	1.4	0.5, 4.3
Paints, inks, and pigments	52	44	0.8	0.5, 1.3	35	27	0.9	0.5, 1.6
Oil-based paints	40	29	1.0	0.6, 1.7	27	14	1.4	0.7, 2.8
Water-based paints	34	28	0.9	0.5, 1.5	24	16	1.1	0.6, 2.2
Metals, alloys, and solders	55	44	0.9	0.6, 1.4	39	22	1.3	0.7, 2.2
Brass	19	8	1.8	0.8, 4.2	8	4	1.5	0.4, 5.2
Bronze	10	5	1.5	0.5, 4.4	4	2	1.4	0.3, 7.9
Galvanized steel	26	17	1.1	0.6, 2.1	18	8	1.6	0.7, 3.9
High-speed steel	11	7	1.2	0.4, 3.1	8	3	2.0	0.5, 7.7
Mild steel	22	16	1.0	0.5, 2.0	15	7	1.6	0.6, 4.0
Stainless steel	24	15	1.2	0.6, 2.3	13	5	1.9	0.6, 5.4
Alloys (NOS‡)	5	7	0.5	0.2, 1.6	3	5	0.4	0.9, 1.7
Metals (NOS)	13	11	0.9	0.4, 2.0	10	3	2.6	0.7, 9.5
Solders (NOS)	25	12	1.6	0.8, 3.3	17	5	2.6	0.9, 7.1
Other								
Cardboard dust	14	15	0.7	0.3, 1.5	11	7	1.1	0.4, 3.0
Flour or starch dust	8	6	1.1	0.4, 3.2	5	3	1.3	0.3, 5.5
Grain dust	9	6	1.1	0.4, 3.3	8	2	3.2	0.7, 15.2
Rubber dust	6	5	0.8	0.2, 2.7	4	1	2.8	0.3, 25.5
Wood dust	47	26	1.4	0.8, 2.3	37	18	1.5	0.8, 2.8
Plastics, synthetics, and resins (NOS)	10	16	0.4	0.2, 1.0	4	5	0.6	0.2, 2.3

* The analysis included 405 case fathers and 302 control fathers.
† Main entries indicate categories of chemicals analyzed as groups (from table 1).
‡ IH, industrial hygienist; CI, confidence interval; NOS, not otherwise specified.
§ Adjusted for child's age, maternal race, maternal age, and maternal education.

finding was not confirmed in another population (1), although more specific self-reported paternal exposure to benzene was associated with neuroblastoma. Although several of the hydrocarbons we studied are suspected carcinogens, the only substance deemed by International Agency for Research on Cancer evaluation to have sufficient evidence of carcinogenicity is benzene (20). Paternal exposures to certain hydrocarbons, including toluene and xylene, have been associated with the risk of spontaneous abortion (21), which may indicate a chemical's ability to affect germ cells or fetal development. Exposure to hydrocarbons is common in occupations for which associations with neuroblastoma have previously been observed, including electrician, electrical assembler and repairer, farmer, mechanic, painter, and glass and optical goods worker (2, 3, 6).

Surveillance has shown cytogenetic, mutagenic, and genotoxic effects of working as a painter (22–26), and evidence of the carcinogenicity of occupational painting is considered sufficient by the International Agency for Research on Cancer (24). In addition, numerous childhood cancer studies have implicated painting as a high-risk occupation (27–34). In our analysis of occupational groups (6), paternal occupation as a painter was associated with a twofold increase in the incidence of neuroblastoma in offspring. However, in analysis of specific chemical exposures, there is little evidence that exposure to paints accounts for this association. The increased rate of neuroblastoma associated with painting as an occupation may instead result from the use of solvents such as lacquer thinner, mineral spirits, paint thinner, or turpentine during the painting process. All of the fathers who worked as painters during the period of interest reported exposure to at least one of these solvents. Indeed, when we adjusted for paternal exposure to these four solvents, the effect estimate for oil-based paint was diminished (OR = 1.0; 95 percent CI: 0.4, 2.5).

Paternal exposures to several metals were associated with an increased rate of neuroblastoma; however, exposures to metals were rather uncommon, and effect estimates were very imprecise. Previous studies of paternal occupation and neuroblastoma observed positive associations with self-reported occupational exposure to metal fumes and dusts (1) and melted metal (5). Potential effects of paternal metal exposures on neuroblastoma are biologically plausible, since several metals are known to be carcinogenic and genotoxic. The International Agency for Research on Cancer has concluded that cadmium, nickel, and hexavalent chromium compounds are definite or probable carcinogens (35–37), and the potential for these metals to cause genetic alterations is clear from the results of in vitro and in vivo assays (38). In addition, a transgenerational carcinogenic effect of chromium was observed among offspring of male rats exposed to chromium trichloride (17). Our previous analysis of paternal occupation did not indicate any increased incidence of neuroblastoma associated with welding occupations that entail high exposure to metal fumes (6), but any risk associated with metal exposure might be in specific types of welding or in grinding and cutting operations that have metal dust exposure. Unfortunately, small numbers of exposed subjects did not permit precise estimation of effects by specific work task.

We observed a positive association with paternal exposure to wood dust. Wood dust is known to be carcinogenic to nasal epithelium (39); however, the systemic carcinogenic potential of wood dust beyond its effect through direct contact with tissues has not been extensively studied. Woods contain numerous chemical components, including terpenes (the major component of turpentine), phenols, resin acids, and miscellaneous inorganic compounds, and an effect of wood dust could potentially operate by a genotoxic mechanism in which the chemicals within the dust mutate germline DNA. Constituents of beech and oak have been shown to cause DNA damage in mammalian cells (39). Apart from the inherent constituents of wood, wood used in construction is often treated with preservatives such as chromated copper arsenate and chlorophenol derivatives, which may contribute to the genotoxicity of wood dust. Workers in carpentry or construction are commonly exposed to a variety of solvents, including naphtha, white spirits, toluene, xylene, benzene, alcohols, and glycol ethers (39). However, the effect estimate for wood dust in our study was unconfounded by exposure to commonly co-occurring solvents and paints.

Our IH review of self-reported exposures allowed us to evaluate the impact of exposure misclassification on calculated effect estimates. If exposure misclassification were nondifferential, the effect estimates reflecting true positive associations should, on average, be biased toward the null for self-reported exposures compared with estimates for IH-reviewed exposures. The estimates for paternal exposures generally followed this expected pattern. However, there is some evidence that exposure misclassification of fathers' reports was differential; exposure reports by control fathers were approximately 70 percent more likely to be recoded as "unexposed" than reports by case fathers. This pattern of differential reporting could account for the generally lower odds ratios observed for self-reported exposures. The results for maternal exposures followed an opposite pattern in that odds ratios for self-reported exposures were generally more elevated than those for IH-reviewed exposures. These results suggest that the exposure misclassification for mothers was perhaps due to recall bias; for example, case mothers may have exaggerated their exposure histories. In fact, exposure reports by case mothers were approximately 60 percent more likely to be recoded as "unexposed" than reports by control mothers.

Because our IH review focused solely on correcting false-positive exposure reports, it is likely that false negatives (i.e., nonreporting) exist in our data. A more extensive review could use information on job duties to correct some of the false negatives. In most cases, however, job duty information is not detailed enough to infer specific exposures and could at best be used to infer exposure to categories of chemicals. For estimation of the prevalence of false negatives and differences in reporting between cases and controls, we conducted a post hoc review to detect unreported exposures to the categories "paints, inks, and dyes" and "metals, alloys, and solders" and to the specific exposure "wood dust." We searched for exposures to paints, inks, and dyes by examin-

ing job duties for anyone classified with an occupation of "painter," as well as by searching for the words "paint," "ink," and "dye" in job duties across all occupations. We searched for exposures to metals, alloys, and solders by examining job duties for anyone classified with an occupation of "welder or cutter," as well as by searching for the words "weld," "metal," "steel," "solder," and "alloy" in job duties across all occupations. We searched for wood dust exposures by examining job duties for anyone classified with an occupation of "carpenter" or "construction worker," as well as by searching for the word "wood" in job duties across all occupations. After searching for the above keywords, we used subjective judgment to decide whether the person's job duty description indicated probable exposure. Out of 2,028 jobs reported by mothers and fathers during the period of interest for which there was exposure information, we found examples of potential false negatives for paints, inks, and dyes (10 jobs (seven fathers)), metals, alloys, and solders (14 jobs (four mothers and eight fathers)), and wood dust (22 jobs (one mother and 20 fathers)). Some of these potential false negatives occurred in jobs where we were confident that exposure had occurred—such as the work of a painter whose job duty was "painting homes" and the work of welders who reported "welding" as their job duty—but some potential false negatives were found among owners, foremen, and laborers whose duties were diverse, so the time spent in the exposed tasks may have been insufficient for us to classify the person as exposed. In many instances, the parents with potential false negatives reported exposure to other chemicals (e.g., a painter reporting exposure to thinner solvents, a welder reporting exposure to cutting oil), providing further indication that their work offered opportunities for exposure (as opposed to simply office work). The majority (75 percent) of fathers with potential false negatives were case fathers, indicating some differential bias. However, when we included these parents in the "exposed" groups of the respective exposure variables, effect estimates were not substantially changed (paternal exposure to paints, inks, and dyes: OR = 1.0; paternal exposure to metals, alloys, and solders: OR = 1.1; paternal exposure to wood dust: OR = 1.7).

An ideal IH review might capture both false-positive and false-negative exposures. It would be fairly simple to capture some false negatives by looking within certain occupations and by searching for keywords; however, there are not many occupations or tasks (such as welding) in which exposure is fairly certain to occur. There is clear exposure variability in most other occupations; for example, dry cleaners may send clothes off-site for cleaning or use nonsolvent cleaning agents, and farmers may not apply their own pesticides or may farm organically. For this reason, a more sensitive data collection system might employ computer-assisted interviews in which certain occupations or keywords would automatically trigger job-specific questions to enhance exposure recall or to elicit information from which specific exposures could be inferred with greater certainty (40).

The data presented here broaden our understanding of the associations between parental occupational chemical exposures and neuroblastoma in offspring in several ways. To our knowledge, this study is the largest study of neuroblastoma conducted to date, with the most detailed information on self-reported occupational exposures. The ability to evaluate actual chemical exposures rather than merely occupations provides guidance for the direction of future research directed toward specific causative agents.

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